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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.  | CONFIRMATION NO. |
|-----------------|-------------|----------------------|----------------------|------------------|
| 09/697,079      | 10/27/2000  | Donna K. Fox         | 0942.4460002/RWE/BJD | 7547             |

26111 7590 09/09/2003

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| EXAMINER |
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JOHANNSEN, DIANA B

|          |              |
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| ART UNIT | PAPER NUMBER |
|----------|--------------|

1634

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                                       |                                   |  |
|------------------------------|---------------------------------------|-----------------------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>09/697,079  | <b>Applicant(s)</b><br>FOX ET AL. |  |
|                              | <b>Examiner</b><br>Diana B. Johannsen | <b>Art Unit</b><br>1634           |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 August 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 45, 49, 52-56 and 59-92 is/are pending in the application.
- 4a) Of the above claim(s) 59-92 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 45, 49, and 52-56 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
     If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
     a) ☐ All    b) ☐ Some \*    c) ☐ None of:  
         1. ☐ Certified copies of the priority documents have been received.  
         2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
         3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
     \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
     a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2003 has been entered.
2. Claims 57-58 have been canceled, and claims 59-92 have been added. Claims 45, 49, 52-56, and 59-92 are currently pending.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Election/Restriction***

4. Newly submitted claims 59-92 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons. The claims under consideration in the instant application (currently claims 45, 49, and 52-56) are drawn to compositions comprising restriction endonucleases and polymerase inhibitors, classified in, e.g., class 530, subclass 388.26. In contrast, the newly added claims are drawn to compositions comprising polypeptides with polymerase activity and DNA modifying enzymes (such as ligases and endonucleases), classified in, e.g., class 435, subclass 194. The newly added claims are drawn to compositions requiring structurally and functionally different molecules than those of claims 45, 49, and 52-56 (specifically,

polymerases in combination with a modifying enzyme such as an endonuclease or ligase, as compared to a polymerase inhibitor in combination with an endonuclease). As the different groups of claims are classified differently, and require separate searches for different types of compositions, examination of the additional inventions of new claims 59-92 would pose a serious burden on the examiner. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 59-92 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

***Claim Rejections - 35 USC § 103***

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 45, 49, and 52-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Todd (WO 96/32500 [10/1996]) in view of Sobol et al (U.S. Patent No. 5,543,296 [8/1996]) and Isner (U.S. Patent No. 5,652,225 [7/1997; effective filing date 10/1994]).

Todd discloses the preparation of compositions for nucleic acid amplification by PCR (see, e.g., page 22). Todd discloses several reagents that are combined during preparation of the PCR reaction mixture, including a restriction endonuclease, anti-*Taq* polymerase antibodies, and multiple buffers (see entire reference, especially p. 19, lines 11-21; page 22, lines 8-21). However, the instant claims require a composition that “does not contain any nucleic acid molecules” (see independent claims 45 and 53). As Todd does not disclose the order in which the reagents of the PCR reaction mixture are combined with one another, Todd does not disclose a composition meeting the requirements of the claims. Sobol et al disclose the use of master mixes of reagents while preparing multiple samples for PCR (col 17, lines 19-44; col 18, lines 25-50). It is well known to those of skill in the art that a master mix is typically employed when performing multiple PCR reactions, in order to improve efficiency. Further, Isner et al disclose that the use of master mixes in the preparation of enzymatic reaction mixtures results in “greater accuracy and reproducibility” (see column 15, lines 37-39). Sobol et al disclose the preparation of a PCR master mix that includes all PCR reagents (including polymerase) other than primers and template (see col 17, lines 19-44; col 18, lines 25-50). In view of the teachings of Sobol et al and Isner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have prepared the PCR reaction mixtures of Todd by first preparing a master mix composition including all reagents other than template and primers, which master mix composition would meet the requirements of the instant claims. An ordinary artisan would have been motivated to have made such a modification for the advantage of

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efficiency, accuracy, and reproducibility in conducting PCR amplification. Further, an ordinary artisan would have been motivated to have prepared a master mix including all reagents but template and primers in order to have possessed a single master mix composition that could be employed successfully with a variety of templates and primers, as exemplified by Sobol et al, for the advantages of convenience and efficiency.

Regarding claim 45 and claims dependent therefrom, it is noted that it is a property of the anti-*Taq* polymerase antibodies disclosed by Todd that they constitute binding proteins. With respect to claim 49, it is noted that the claim is sufficiently broad so as to encompass storage under any type of conditions for any length of time, and it is an inherent property of the master mix suggested by Todd in view of Sobol et al and Isner that it would be "stable upon storage" under appropriate conditions (e.g., in a freezer).

In the Amendment and Reply filed August 11, 2003, the response traverses the rejection on the following grounds. Applicants argue that "a reason, suggestion, or motivation" to combine the cited references is lacking, and that the examiner has not established a *prima facie* case of obviousness. The response argues that Todd does not disclose a combination lacking nucleic acid molecules, or the use of master mixes. The response further argues that Sobol "does not disclose the preparation and use of compositions comprising a restriction endonuclease," and that therefore "Todd in combination with Sobol does not disclose or suggest a composition meeting the requirements of the claims." Applicants also urge that Isner "does not specifically

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disclose what reagents are included" in master mixes, and that "one of ordinary skill could have found no disclosure in Isner that would have been sufficient to provide the missing components from the compositions of Todd and Sobol, alone or in combination." Further, the response argues that information in the cited references would not have motivated one of ordinary skill to prepared the claimed compositions, particularly because "the referenced cited by the Examiner relating to 'master mixes' have nothing to do with, and do not include, restriction endonucleases."

Applicants' arguments have been thoroughly considered but are not persuasive. First, it is noted that the motivation to combine the cited references is that which was previously stated in the rejection of the prior Office action (which rejection is repeated above). Particularly, both the knowledge generally available to one of ordinary skill that master mixes are typically employed when performing multiple PCR reactions in order to improve efficiency, as well as the disclosure in the Isner et al reference that the use of master mixes results in "greater accuracy and reproducibility," would have provided motivation to one of ordinary skill to employ a master mix when setting up the reactions of Todd. It is acknowledged that because Todd does not disclose the order in which reagents are combined, Todd does not disclose a combination meeting the requirements of the claims. However, given this lack of guidance in the Todd reference with respect to manner and order in which to combine reagents, one of ordinary skill would have relied on well-known and reliable methods – such as the use of a master mix of enzymes and buffers prepared prior to addition of the primers and templates needed for each individual amplification – for the advantages of efficiency, accuracy,

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and reproducibility in effecting amplification, as suggested by Sobol et al and Isner et al. Further, it is noted that the Sobol et al reference was not cited for any teaching of a composition including an endonuclease, but was cited for its teaching of a master mix comprising all reagents other than primers and template in the practice of PCR. Additionally, the Isner et al reference was cited for its disclosure that the use of master mixes improves accuracy and reproducibility, not for any teaching of the particular reagents that would be included in a specific master mix (which would clearly depend on the nature of the reaction being performed). Accordingly, Applicants arguments are not persuasive.

### ***Conclusion***

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.



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A handwritten signature in black ink, appearing to read "Diana B. Johannsen". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Diana B. Johannsen  
September 7, 2003